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Atty. Dkt. No. 076333-0325

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Louis D. Falo *et al.*
Title:	INDUCTION OF TUMOR AND VIRAL IMMUNITY USING ANTIGEN PRESENTING CELL CO-CULTURE PRODUCTS AND FUSION PRODUCTS
Appl. No.:	10/608,424
Filing Date:	6/30/2003
Examiner:	Gerald R. Ewoldt
Art Unit:	1644
Confirmation Number:	8081

BRIEF ON APPEAL AND RESPONSE TO NOTICE OF NON-COMPLIANT APPEAL BRIEF

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Sir:

This appeal brief was originally filed on January 25, 2007, along with the $250.00 appeal fee prescribed by 37 C.F.R. 41.20(b)(2) and a Petition for Extension of Time. In response, the Office issued a Notification of Non-Compliant Appeal Brief dated March 30, 2007. Although Appellants believe that the original appeal brief was fully compliant, Appellants file the present appeal brief. The present appeal brief is identical in substance to the January 25th appeal brief, except that changes are made in the Summary of the Claimed Subject Matter section starting on page 1 to address the March 30th Notification.

Appellants do not believe that any fees are presently due. However, if any fees necessary to timely file this appeal brief are deemed insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

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REAL PARTY IN INTEREST

The real party in interest is the University of Pittsburgh, the assignee of this application.

RELATED APPEALS AND INTERFERENCES

As to an appeal or interference that may directly affect, be directly affected by, or have a bearing on the Board's decision in present appeal, Appellants are aware only of an appeal pending in relation to an application, serial No. 09/208,549 (Atty. Dkt. No. 076333-0242), that is related, as a divisional, to the above-captioned application. The issues presented in the appeal of the '549 application are entirely distinct from those of the present appeal.

STATUS OF CLAIMS

Claims 1, 2, and 4-12 are pending and subject to examination on the merits. Claims 3 and 13-26 were canceled previously.

STATUS OF AMENDMENTS

Appellants made no amendments after the Final Office Action mailed January 26, 2006. All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

Two independent claims, claims 1 and 8, are on appeal. Applicants provide below "a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number." *See* 37 C.F.R. § 41.37.

Claim 1 relates to a formulation comprising at least one hybridoma that is the fusion of at least one antigen presenting cell and at least one virally infected cell. *See* specification at page 3, line 30 – page 4, line 4; page 4, lines 10-15; page 6, lines 9 and 10; page 8, lines 3-6. The antigen presenting cell can be a macrophage or a dendritic cell. *Id.* at page 7, lines 15-

17. The specification explains that these formulations can be used to treat viral infection by inducing cytotoxic T-lymphocytes (CTLs). *Id.* at page 4, lines 5-22.

Claim 8 further relates to a pharmaceutical composition comprising a hybridoma, as claimed in claim 1, and a suitable pharmaceutical carrier. *Id.* at page 3, line 30 – page 4, line 4; page 4, lines 10-12; page 6, lines 9 and 10; page 8, line 32 – page 9, line 6. The specification explains that these formulations can be used to treat viral infection by inducing cytotoxic T-lymphocytes (CTLs). *Id.* at page 4, lines 5-22.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

This appeal presents a single ground of rejection for review.[1] Specifically, Appellants present for consideration the rejection of claims 1, 2, and 4-12 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

ARGUMENT

The specification contains a complete description of the claimed invention, sufficient to allow one skilled in the relevant art to make and use the claimed invention without undue experimentation, as evinced by the working examples and corroborative literature. The Examiner's arguments to the contrary are critically flawed.

The examiner argues that the specification fails to enable how to *make* claimed invention. This argument fails because it is premised on the wrong standard for determining enablement. Specifically, the examiner imposes the requirement that the hybridoma be "immortal." Yet, the "invention that one skilled in the art must be enabled to make and use is

[1] The Final Office Action also provisionally rejected claims 1, 2, and 4-12 over claims 1, 2, and 4-12 of co-pending serial No. 11/089,035 (Atty. Dkt. No. 076333-0366). Appellants need not address this rejection here, however, because of its provisional nature.

that defined by the claim(s)," and the appealed claims do not require the "hybridoma" to be "immortal." MPEP § 2164.

The examiner also argues that the specification fails to enable a skilled artisan to *use* the claimed invention, because the invention allegedly cannot be used to treat HIV infection without undue experimentation. This argument fails for two separate reasons. First, the examiner improperly has discounted evidence proving that the claimed invention is enabled. Thus, the examiner has failed to consider the evidence as a whole, as he is required to do. *In re Wands*, 858 F.2d at 731, 737, 8 USPQ2d 1400, 1407. Second, the examiner has failed to demonstrate that the entire claim scope is enabled. Instead, the examiner focuses on the alleged lack of enablement of a single embodiment, curing HIV. Even were the single embodiment not enabled, as the examiner contends, it still would be the case that the "presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." MPEP § 2164.08(b); *see also Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 USPQ.2d 1078, 1085 (Fed. Cir. 2005); *In re Angstadt*, 537 F.2d 498, 503, 190 USPQ 214, 218 (CCPA 1976). Here, there is no evidence or explanation that it would require undue experimentation to identify any inoperative embodiments.

A. The Specification Enables One Of Skill In the Art To Make The Claimed Invention (Claims 1, 2, and 4-12)

The specification contains sufficient guidance to make the claimed invention without undue experimentation. The claims are drawn to a formulation and pharmaceutical composition comprising "at least one hybridoma having at least one first cell fused to at least one second cell." The first cell is an antigen presenting cell (APC) selected from a macrophage and a dendritic cell (DC), and the second cell is a "virally infected cell." The specification teaches that "the hybridomas ... of the present invention can be formed by any

method known in the art." Specification at page 8, lines 3-4. Indeed, methods were well-known in the art for fusing antigen presenting cells, such as dendritic cells and macorphages, to other cells. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) (noting that a specification preferably omits what is known in the art). The specification goes on to provide a method for forming a hybridoma from an APC and virally infected cell, using polyethylene glycol (PEG). *Id.* at page 8, lines 4-11. Moreover, the specification contains working examples demonstrating the formation of a hybridoma. *Id.* at page 11, lines 5-19. Thus, the specification provides guidance as to how to construct the claimed formulation.

The Examiner does not dispute that the recited APCs can be fused with a "virally infected cell." Instead, he invokes literature citations to import a limitation into the claims, thereby to validate a conclusion of non-enablement. In particular, the Examiner relies on literature references to argue that a "hybridoma" is a cell line in "a state of unrestrained growth in culture, resembling or identical with the tumorigenic condition." Office Action at 3.[2] So saying, the Examiner purports to find in the present recitation of "hybridoma" a requirement for an "immortal" cell, and then judges enablement with reference to that requirement. *Id.*

But the claims do not require the hybridoma to be an immortal cell. "An applicant is entitled to be his or her own lexicographer," and "[w]here an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim." MPEP § 2111.01(IV); *see Toro Co. v. White Consolidated Industries Inc.*, 199

[2] Unless otherwise states, citations to "Office Action" are to the Final Office Action dated January 26, 2006.

F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings"). Here, the specification defines a hybridoma as "a physical combination of at least two different cell types." Specification at page 6, lines 14-15. In other words, the hybridoma is simply a fusion of at least two different cell types. The specification further specifies that the two different cell types can be "at least one APC and at least one virally infected cell." *Id.* at page 6, lines 15-18. Nothing in the specification requires the "hybridoma" to be an immortal cell. Indeed, the examiner does not rely on the specification to define a "hybridoma" as an immortal cell and instead resorts to literature references to import a requirement into the claims. Thus, it is improper to require enablement of an immortal "hybridoma" even assuming, *arguendo*, that one of skill in the art understands a "hybridoma" to be an immortal cell.

B. One Of Skill In The Art Could Use The Claimed Invention Without Undue Experimentation (Claims 1, 2, and 4-12)

"[W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." MPEP § 2165.02(c). "In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *Id.* Here, the specification readily satisfies this standard.

The specification teaches that the claimed formulation and composition can "protect against the viral infection caused by the virally infected cells used in the formulation, and/or provide therapeutic relief from patients having such viral infections." Specification at page 4, lines 2-4. The specification explains that while virally infected cells can express antigens which can be targeted by cytotoxic T-lymphocytes (CTLs), the virally infected cells

themselves do not stimulate immunity. *Id.* at page 4, lines 5-7. This lack of immunity stems from the inability of virally infected cells to express the antigens in the appropriate context of co-stimulation. *Id.* at page 4, lines 7-9. The claimed invention overcomes this problem by fusing the virally infected cell to APCs, which express co-stimulatory molecules and cytokines. Because the fusions exhibit the properties of both the APC (expression of co-stimulatory molecules and cytokines) and the virally infected cell (expression of antigen), the fusions stimulate immunity and "result in the destruction of the virus." *Id.* at page 4, lines 17-22. The specification goes on describe in more detail how the claimed formulations and compositions can be used to treat viral infections. *See, e.g., id.* at pages 8-10. For instance, the specification teaches that the "effective amount" of the composition will vary depending on the patient and severity of the infection. Generally, however, the dosage will be about 1 x 10^6 cell equivalents to about 100 x 10^6 cell equivalents per treatment. *Id.* at page 10, lines 7-10. Thus, the specification teaches how the claimed invention is therapeutically useful by virtue of its ability to destroy virus.

The working examples corroborate the teachings of the specification and demonstrate that the claimed fusions are therapeutically useful. Indeed, the examples demonstrate that "immunization with products of [dendritic cell]-tumor cell fusions or co-cultures can induce tumor-specific CTLs and potent protective anti-tumor immunity against two distinct, poorly immunogenic tumors." Spec. at page 17, lines 3-6. In addition, the fusions were shown to eradicate existing tumors. *See* example 6 (page 17).

While the examples were directed to tumor cells rather than virally infected cells, there is no objective reason to doubt that the results would be similar for virally infected cells, because the same mechanism applies. Namely, the fusions combine the ability of APCs to

express co-stimulatory molecules and cytokines with the ability of tumor and virally infected cells to express antigen.

Indeed, a literature reference confirms the teachings of the specification also apply to virally infected cells. Specifically, Marañón *et al.*, *Proc. Nat'l Acad. Sci.* USA 101: 6092-97 (2004), studied the presentation of HIV antigens from dendritic cells and concluded that dendritic cells that present viral antigens stimulate virus-specific CD8+ cells. In fact, Marañón concluded that dendritic cell antigen presentation could be "exploited to eradicate latently infected reservoirs." Marañón, abstract (emphasis added). Thus, Marañón confirms that the claimed invention could be employed in the treatment of viral infections, including HIV infection.

The Examiner contends that undue experimentation is required to use the claimed invention, because the claimed formulations are "highly unpredictable" and "would be more likely to exacerbate viral infections than to treat or prevent them." Office action at 3. As support for this contention, the examiner cites publications generally relating to HIV: Frank, *Current Mol. Medicine* 2: 229 (2002); Cohen, *Science* 295: 1616 (2002); Roberts, *The Scientist* 18(11) (June 2004).

The Examiner's conclusion is flawed for at least two reasons, however. First, the Examiner improperly discounts evidence, Marañón, demonstrating that the claimed invention could be useful in treating viral infections, including HIV. Second, even if one assumes that the claimed invention is not enabled for treating HIV, claims 1-2 and 5-12 are not necessarily defective under Section 112, first paragraph, because "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." MPEP § 2164.08(b).

1. Marañón Provides Evidence Of Enablement (Claims 1, 2, and 4-12)

Marañón demonstrates that DCs presenting HIV antigen could be "exploited to eradicate latently infected reservoirs," as discussed above. The examiner improperly dismisses Marañón.

At the outset, the examiner argues that Marañón is "not of record in this case and thus, need not be addressed." This is not correct. Marañón was first cited in Appellants' response of November 7, 2005, to the non-final Office Action dated June 7, 2005. Marañón was submitted to counter the Examiner's argument, presented in the June 7 Office Action, that the claims lack enablement. Thus, Marañón was timely submitted as evidence directed to an issue of patentability raised in the June 7th Office Action. Accordingly, MPEP § 609.05(c) compels its consideration by the Examiner.

The Examiner also argues that Marañón "cannot be used to establish the enablement of the instant application as of its priority date," because it was published "seven years after the priority date of the instant application." Office Action at 4. In addition, the examiner notes that Marañón "employs live antigen-loaded dendritic cells and not the fusion products of the instant claims" and that Marañón "addresses a number of issues that were clearly not known as of the priority date of the instant application." Office Action at 4.

These reasons for discounting Marañón are inapposite to Marañón's value in demonstrating the enablement of the claimed invention. It is well-established that a post-filing date reference can be used to demonstrate enablement when the reference merely demonstrates the state of the art as of the priority date. *See , e.g., Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ.2d 1302, 1305 (Fed. Cir. 1987). Marañón does precisely that,

employing the same general approach that Appellants described in their application and demonstrated successfully.

In challenging this proposition, the Examiner notes "issues that were clearly not known as of the priority date."[3] These "issues" had no bearing, when the invention was made, on what level of experimentation the skilled person needed to implement Appellants' teachings in the present specification. For instance, the Examiner argues that one of the allegedly unknown issues was "the manner in which dendritic cells take up and present antigens." Office Action at 4. Yet, one of skill in the art would not need to understand the mechanism of antigen presentation in order practice the claimed invention. In other words, operational sufficiency does not require an understanding of the theoretical underpinnings of the operation.

Finally, the fact that Marañón used antigen-loaded dendritic cells, rather than fusion products, in no way detracts from the probity of Marañón in vindicating the enabled quality of the appealed claims. Simply put, the Examiner has proffered no evidence or explanation why the results obtained from using fusion products would differ from results obtained using Marañón's co-culture cells. Thus, the Examiner has failed to satisfy his evidentiary burden. Moreover, the Examiner cannot satisfy his evidentiary burden on this point, because Appellants' working examples demonstrate the success of both fusion and co-culture techniques. Thus, Appellants' working examples directly contradict the Examiner's efforts to discount Marañón. Accordingly, the examiner improperly dismissed Marañón in rejecting the present claims as allegedly lacking enablement.

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[3] While the Examiner contends that Marañón addresses "issues that were clearly not known as of the priority date," the Examiner identified only a single issue, the mechanism by which DCs "take up and present antigens." Office Action at 4.

2. The Examiner's Arguments Fail To Demonstrate The Enablement Of The Entire Claim Scope (Claims 1-2 And 5-12)

Even if taken as true, the examiner's arguments fail to satisfy the burden in establishing a rejection of lack of enablement for claims 1-2 and 5-12. The examiner focuses almost exclusively on HIV with some passing reference to other viruses, but claims 1-2 and 5-12 are not directly exclusively to HIV. Instead, they generally cover "virally infected cells." Thus, at best, the examiner has identified only a single inoperative embodiment. Such a showing is not sufficient to reject the claims as lacking enablement, because "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 USPQ.2d 1078, 1085 (Fed. Cir. 2005); *see also Application of Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1071) (holding that claims reading on "very large number of inoperative embodiments" enabled because inoperative embodiments could be readily identified); *In re Angstadt*, 537 F.2d 498, 503, 190 USPQ 214, 218 (CCPA 1976); MPEP 2164.08(b). Thus, even if one assumes, *arguendo*, that the specification fails to enable treatment of HIV using the claimed formulation, such a showing does not demonstrate that the claims lack enablement.

C. Conclusion

Appellants respectfully request that the rejection of claims 1, 2, and 4-12 be reversed, because a proper analysis of the evidence as a whole fails to establish that the claims lack enablement.

Respectfully submitted,

Date January 25, 2007

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CLAIMS APPENDIX

1. (Previously Presented) A formulation comprising at least one hybridoma having at least one first cell fused to at least one second cell; wherein said first cell is an antigen presenting cell selected from the group consisting of a macrophage and a dendritic cell, and said second cell is a virally infected cell.

2. (Previously Presented) The formulation of claim 1, wherein said dendritic cells are selected from the group consisting of cutaneous epidermal Langerhans cells, dermal dendritic cells, lymph node dendritic cells, spleen dendritic cells and dendritic cells derived through in vitro culture of precursors.

3. (Canceled).

4. (Previously Presented) The formulation of claim 1, wherein said virally infected cells are selected from the group consisting of cells infected with influenza virus, human immunodeficiency virus, cytomegalovirus, human papilloma virus and herpes simplex virus.

5. (Previously Presented) The formulation of claim 1, wherein said hybridoma contains a ratio of first cells to second cells between about 1:100 and 100:1.

6. (Previously Presented) The formulation of claim 1, wherein said hybridoma contains a ratio of first cells to second cells of between about 1:10 and 10:1.

7. (Previously Presented) The formulation of claim 1, wherein said hybridoma contains a ratio of first cells to second cells of about 6:1.

8. (Previously Presented) A pharmaceutical composition comprising: at least one hybridoma; and a suitable pharmaceutical carrier; wherein each hybridoma is comprised of at least one first cell fused to at least one second cell; wherein said first cell is

an antigen presenting cell selected from the group consisting of a macrophage and a dendritic cell, and said second cell is a virally infected cell.

9. (Previously Presented) The pharmaceutical composition of claim 8, wherein said suitable pharmaceutical carrier is selected from the group consisting of saline and phosphate buffered saline.

10. (Previously Presented) The pharmaceutical composition of claim 8, wherein said hybridomas have a ratio of first cells to second cells of between about 1:100 and 100:1.

11. (Previously Presented) The pharmaceutical composition of claim 8, wherein said hybridomas have a ratio of first cells to second cells of between about 1:10 and 10:1.

12. (Previously Presented) The pharmaceutical composition of claim 9, wherein said hybridomas have a ratio of first cells to second cells of about 6:1.

13-36. (Canceled).

EVIDENCE APPENDIX

Marañón *et al.*, PNAS 101(16):6092:97 (2004) – Marañón was cited in Appellants' response of November 7, 2005 at page 6.

RELATED PROCEEDINGS APPENDIX

No decisions have been issued in Appl. No. 09/208,549 (Atty. Dkt. No. 076333-0242). Thus, there are no copies of decisions to provide in this section.